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Paediatric Tumours in the Adult Population: The Experience of the Royal Marsden Hospital 1974–1990

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Adult patients (greater than 18 years), referred to the Royal Marsden Hospital between 1974 and 1990 with embryonal tumours, have been reviewed. The aim of the study was to document the presentation, management and outcome for this group of patients and to compare these parameters with those of tumours of the same histology arising in the paediatric population.

The study population consisted of 15 patients with medulloblastoma, 15 with Ewing's sarcoma, three with neuroblastoma, seven with rhabdomyosarcoma and two with nephroblastoma. Actuarial survival, at 5 years, for adults with medulloblastoma was 80%, which compares very favourably with the outcome for children treated over the same time span. In addition, salvage therapy after relapse was in some cases successful. In the Ewing's sarcoma group the outcome was less favourable, with 5-year actuarial survival of 50%. This is disappointing in view of the lack of tumours with poor prognostic features and may be an area in which these tumours differ from those that arise in children. The number of patients with the diagnosis of neuroblastoma, rhabdomyosarcoma and Wilms' tumour was too small for statistical analysis and they are presented as case reports.

Embryonal tumours arising in adults provide an opportunity to study clinical behaviour and biology from an extreme standpoint. This may provide useful information with regard to aetiology, natural history and treatment response. The establishment of registers facilitate the collection of relevant data and also offers the opportunity to improve the treatment received by patients with these rare tumours.

Key words: embryonal tumors, adults, medulloblastoma, Ewing's sarcoma

INTRODUCTION

Embryonal tumours usually occur in the paediatric age group and are a rare occurrence in adults. Within the paediatric oncology population, there are definite and separate peak age incidences for different embryonal tumour types. This means that their occurrence in adults (> = 18 years) will be more likely for some tumour types than for others. For example, the peak age incidence for Ewing's sarcoma being between 10 and 15 years makes this tumour much more likely to encroach on the adult population than one such as Wilms' where the peak is from 1 to 5 years.

Although acknowledgeably rare, the true incidence of embryonal tumours in the adult population is uncertain. The reasons for this include problems with diagnostic criteria, occasional reporting of individual or small numbers of cases and the lack of any registration system. An exception to the latter is Wilms' tumour where, in the United States, the National Wilms Tumour Study Group (N.W.T.S.G.) has extended data collection to include adults as well as children [1].

The occurrence of an embryonal tumour in an adult patient usually poses a management problem. This arises as a result of the rarity of the diagnosis by adult oncologists, scarcity of published data on management and outcome, and because of the problems encountered when applying paediatric treatment regimens to older patients.

The occurrence of an embryonal tumour in an adult patient also raises interesting biological and aetiological issues. Inclusion of this end of the age spectrum in clinical and biological analyses might contribute to our understanding of aetiology and natural history of these tumour types.

The aim of the present study was to review presentation, management and outcome for patients aged 18 years

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or over, treated at the Royal Marsden Hospital between 1974 and 1990 with a diagnosis of medulloblastoma, Ewing's sarcoma, neuroblastoma, Wilms' tumour and rhabdomyosarcoma (alveolar and embryonal). The study was confined to this era because of the widespread use of combination chemotherapy from the mid-1970s onwards, making a more meaningful comparison between adult and paediatric practice.

PATIENTS AND METHODS

All patients referred to the Royal Marsden Hospital between 1974 and 1990 with a diagnosis of medulloblastoma, Ewing's sarcoma, neuroblastoma, Wilms' tumour or rhabdomyosarcoma (alveolar or embryonal type) were identified from the histopathological databases. Those aged 18 years or over at presentation were selected for analysis by a review of case notes. The method of identification of patients means that the histopathology for all cases in this series was reviewed at the Royal Marsden at some time.

Presenting features, management of disease, patterns of relapse and outcome were documented. Due to the rarity of these malignancies the number of patients is small and the results for neuroblastoma, Wilms' tumour and rhabdomyosarcoma are presented as case reports. The number of patients with medulloblastoma and Ewing's sarcoma were sufficient to permit further analysis.

RESULTS

Medulloblastoma

Presenting features. During the study period, 15 adult patients with a diagnosis of medulloblastoma presented to the hospital, their ages ranging from 18 to 54 years with all but four patients aged less than 30 years. During the same time interval 68 patients with medulloblastoma were treated in the Paediatric Department. In the adult group, the commonest presenting symptoms was headache (12 out of 15) followed by nausea and vomiting (9 out of 15), whereas unsteady gait occurred in only six of the patients and cranial nerve palsies in four. The majority of tumours (11) were located in one or other cerebellar hemisphere with only four being described as midline. The median length of history at the time of operation was seven and a half weeks. Twelve patients were male and three female.

Management

All patients underwent posterior fossa exploration with total or subtotal macroscopic excision. The presence of malignant cells in the cerebrospinal fluid was not routinely recorded, either at the time of surgery or during the postoperative staging, and myelography was not routinely performed. Nevertheless, in those patients in whom these investigations were done, all seven had a negative myelogram and a cerebrospinal flow (CSF) result was recorded for five of these which was positive in two patients. A further one patient has CSF cytology alone which was positive. The details available do not permit Chang staging [2].

All patients received postoperative radiotherapy to the whole neuraxis with a boost to the posterior fossa. The posterior fossa dose ranged from 50 to 60 Gy in 1.67 Gy fractions with the remainder of the neuraxis receiving at least 30 Gy given as 1.2 Gy daily fractions to the spinal cord. All radiotherapy was given on a 6 MeV linear accelerator with daily treatment of all fields.

All patients were considered for systemic chemotherapy and all but one went on to receive it. This was generally "sandwiched" between surgery and radiotherapy but was also planned to continue during, and after, radiotherapy. The chemotherapy received by each patient is outlined in Table I.

Postradiotherapy maintenance chemotherapy had to be modified in many cases. Six patients received two cycles and treatment then had to be stopped due to myelosuppression. None of the remaining seven patients received maintenance chemotherapy, two due to myelosuppression, two due to poor general condition, two were from overseas and one refused.

Outcome Following Primary Management

The actuarial 5-year survival for this group of adult patients is 80% (95% confidence interval 50%–93%). Three patients have died and the range of follow-up in survivors is from 1 year 7 months to 14 years 5 months, with a median of 4 years 11 months. Of those six patients who received at least five cycles of maintenance chemotherapy, all remain relapse-free in complete remission from 21 months to 14 years 5 months after treatment (Table II). Of the three patients who could not tolerate maintenance chemotherapy due to low white count, one remains in complete remission 5 years 5 months after treatment and the other two have relapsed with salvage attempted in both cases (see below). Both patients who did not receive maintenance chemotherapy and live abroad have relapsed. One returned to this country for treatment. The patient who refused maintenance chemotherapy remains well. The two patients in poor general condition progressed on treatment and died within months. The final patient who was treated with radiotherapy alone also relapsed and salvage therapy was attempted.

Management of relapsed patients. Of the four patients in whom salvage chemotherapy was attempted, two had relapsed in the bone marrow only and two at the primary site with neuraxis dissemination. The times to

TABLE I. Management of Medulloblastoma Patients

Age at presentation	Chemotherapy given preradiotherapy[a]	Chemotherapy given postradiotherapy
18	procarbazine, methotrexate, vincristine	none
18	procarbazine, methotrexate, vincristine	7 cycles CCNU + vincristine
18	weekly vincristine	6 cycles CCNU + vincristine
20	weekly vincristine	6 cycles CCNU + vincristine
21	weekly vincristine	none
23	procarbazine, methotrexate, vincristine	2 cycles CCNU + vincristine
24	weekly vincristine	none
25	none	none
26	none	6 cycles CCNU + vincristine
27	cisplatin + vincristine	none
28	weekly vincristine	9 cycles CCNU + vincristine
35	weekly vincristine	none
36	weekly vincristine	none
40	none	6 cycles CCNU + vincristine
54	weekly vincristine	none

[a]Chemotherapy was given for two cycles before radiotherapy and where vincristine was prescribed it was normally continued weekly during radiotherapy.

relapses were 13 months; 15 months; 23 months; and 11 years 9 months.

In one patient, resection at the primary site was performed prior to receiving six cycles of VAC (vincristine 2 mg, adriamycin 40 mg/m^2 and cyclophosphamide 600 mg/m^2) followed by radiotherapy 10 Gy in 10 fractions to the spinal cord and posterior fossa with a 15 Gy in 12 fraction boost to the latter site. This resulted in improvement, but not resolution, of the spinal deposits, and disease remains controlled. The two patients with bone marrow relapse also received VAC, one for six cycles with the "eight in one" schedule inserted after cycle three and one received three cycles of VAC followed by five further cycles in which etoposide was substituted for cyclophosphamide. Both patients responded, with repeat marrow aspirates being negative for malignant cells. Both patients went on to receive high dose melphalan (200 mg/m^2) with autologous bone marrow rescue; no problems were noted with engraftment. All three patients remain well with 16 months; 2 years 6 months; and 3 years 2 months of follow-up, although the first has a persistently abnormal myelogram. The fourth patient with central nervous system (CNS) relapse received local radiotherapy to the lumbar sacral spine but his neurological state deteriorated. He was treated with single agent cisplatin, 100 mg/m^2, but his disease progressed and he died.

Quality of life in survivors. All 10 long-term survivors have minimal neurological deficit. Three have suffered psychological problems and anxiety since treatment. At least four are back at work and one is being retrained for nonmanual work; one is at university and another has had a successful pregnancy and is able to look after her family.

Ewing's Sarcoma

Presenting features. During the study period, 15 patients, aged over 18 years, with a diagnosis of Ewing's sarcoma were treated at this hospital, compared with 45 patients treated in the Paediatric Department. Of the 15, 10 were male and five were female. The age range was 18–24 years with three patients aged over 30 years. Four patients presented with extraosseous disease; one had a soft tissue mass in the region of the scapula and one the forearm; the third patient had pleural disease and the fourth a lung primary. Eight patients had disease of the central skeleton at presentation (two spinal vertebrae, two scapula, one sternum, one rib, one sacroiliac region and one hip and iliac region. None had bulky pelvic disease). Only three patients presented with disease of the peripheral skeleton, two in the fibula and one in the tibia. Ten patients had disease localised to the primary site and five patients had metastatic disease at presentation to sites such as lymph nodes and bone marrow. In some of the latter it was difficult to identify the primary lesion.

Management

All patients underwent surgery at the time of diagnosis. In seven cases this consisted of biopsy only but excision was attempted in eight patients and thought to be complete in seven of these (Table II). All patients received radiotherapy as part of primary management except the patient with a lung primary, in whom a watch policy was adopted. Nine patients received at least 50 Gy

TABLE II. Adult Ewing's Sarcoma Patients: Clinical and Management Features

Age	Primary site	Metastasis	Surgery	Radiotherapy	Systemic therapy[a]
18	rib	bone marrow	biopsy	60 Gy	5 cycles post-RT[b]
20	left fibula	—	complete excision	60 Gy	5 cycles pre-RT 3 cycles post-RT
20	vertebrae	para-aortic nodes	biopsy	16 Gy in 4 fractions	Multidrug chemotherapy post-RT then BMT[c]
20	left sacroiliac area	—	biopsy	54 Gy	1 cycle pre-RT 3 cycles post-RT
22	right lung	—	pneumonectomy	—	—
22	left scapula (soft tissue)	—	complete excision	60 Gy	6 cycles pre-RT
22	right tibia	—	biopsy	50 Gy	—
24	left scapula	solitary lung	excision of primary	46 Gy (to primary)	6 months multidrug chemotherapy post-RT
24	right forearm (soft tissue)	—	complete excision	55 Gy	Multidrug chemotherapy RT sandwiched
24	left pleura	lung and lymph nodes	biopsy	24 Gy in 16 fractions	4 cycles then BMT pre-RT
26	left hip and iliac region	bone marrow	biopsy	dose not known	8 cycles pre-RT
32	left scapula	—	incomplete excision	55 Gy	8 cycles post-RT
32	sternum	—	biopsy	64 Gy	6 cycles epirubicin pre-RT
33	thoracic spine	—	complete excision	35 Gy	11 cycles post-RT
34	left fibula	—	complete excision	60 Gy	7 cycles 4 pre- 3 post-RT RT

[a]Systemic therapy, VAC or similar regimen except where stated.
[b]RT, Radiotherapy, fraction size 2 Gy except where stated.
[c]BMT, Bone marrow transplant.

(50–60 Gy in 2 Gy daily fractions). Four patients including those with spinal disease received less (range 16 Gy in 4 Gy fractions to 35 Gy in 2 Gy fractions) and the dose is unknown for one patient (radiotherapy given elsewhere).

Twelve patients received combination chemotherapy as part of their primary management. Two of the 12 were originally misdiagnosed, and therefore their initial chemotherapy was not ideal; both were later switched to a more appropriate regimen. This usually consisted of VAC, or some modification thereof, given for 4–11 cycles. Additional details about VAC modifications included as follows: six patients received combination chemotherapy other than VAC. One patient received ifosfamide rather than cyclophosphamide for three of five cycles and another received the four-drug regimen, Ifosfamide, vincristine, adriamycin and actinomycin D for all seven cycles. Two patients received complex alternating regimens with additional drugs. However, two patients, both with advanced disease at presentation, were thought to be poor risk and received more intensive chemotherapy regimes, followed by high dose melphalan (200 mg/m^2) with autologous rescue. A further was managed with single agent epirubicin. Two patients were not given chemotherapy as part of their primary management.

Outcome

Of the two patients who did not receive chemotherapy, one, with disease in the tibia, is free of disease and one, who underwent pneumonectomy, relapsed in the lung 5 years out from surgery. The latter patient underwent resection and was treated on the "St. Jude's protocol" [4] but progressed and died. Only two of the remaining 13 patients continue in complete remission. Both had complete surgical excision; the first had disease in the thoracic spine managed with radiotherapy followed by 11 cycles of VAC, the second, having extraosseous disease of the left scapula, was managed with radiotherapy (60 Gy in 30 fractions) and six cycles of VAC. The 12 other patients are known to have progressed, and salvage treatment, often aggressive, has been uniformly unsuccessful although three patients with disease were still alive at the

time of analysis. The actuarial 5-year survival is 50% (95% confidence interval 22%–73%). Nine patients have died and the range of follow-up in survivors is from 1 year 3 months to 16 years 10 months with a median of 8 years 1 month.

Neuroblastoma

There were three adult patients treated during the study years, compared with 96 patients treated by the Paediatric Department. All three patients were stage IV at presentation and initial surgery consisted of biopsy only.

Case 1. A 33-year-old male presented with a retroperitoneal mass and multiple liver metastases. He was treated with six cycles of OPEC (vincristine, cisplatin, etoposide, cyclophosphamide) chemotherapy with a partial response, and then underwent debulking of the retroperitoneal mass. High dose melphalan (140 mg/m^2), with autologous bone marrow transplant, was then given with no further response. After one year his disease progressed at multiple sites. He was then treated with various palliative therapies, including mIBG (meta-iodobenzylguanidine) and died 3 years after initial treatment.

Case 2. A 24-year-old male presented with pain in his thigh. Although no primary site was found, the diagnosis was made on bone marrow examination and raised levels of primary catecholamines. He was treated with combination chemotherapy consisting of cisplatin, VM26, adriamycin, vincristine and cyclophosphamide for six cycles, followed by high dose melphalan (140 mg/m^2) and autologous bone marrow transplant. He achieved partial remission for 8 months but his disease subsequently progressed and he died 15 months post-treatment.

Case 3. A 24-year-old female presented with an adrenal primary, positive bone marrow and a pleural effusion. She received chemotherapy similar to case 2 for five cycles, again followed by high dose melphalan (170 mg/m^2) and autologous bone marrow transplant. The adrenal mass decreased in size and she underwent surgical debulking. Unfortunately she relapsed 4 months later and died 1 year after initial treatment.

Rhabdomyosarcoma

Two adults were treated for alveolar rhabdomyosarcoma during the study years and five for embryonal rhabdomyosarcoma. This compares with a combined total of 106 cases seen by the Paediatric Department.

Alveolar rhabdomyosarcoma. ***Case 1.*** An 18-year-old male patient presented with perianal disease (SIOP stage 1) [5] and underwent subtotal resection. He then received seven cycles of IVA (ifosfamide 5 G/m^2, adriamycin 40 mg/m^2, vincristine 2 mg) with a course of local radiotherapy to 44 Gy after four cycles. He relapsed 2 years after treatment at multiple sites and died 3 months later.

Case 2. An 18-year-old patient presented with a paratesticular alveolar rhabdomyosarcoma with ipsilateral nodal involvement in the para-aortic, iliac and supraclavicular nodes, SIOP stage I. He received six cycles of VAC chemotherapy and had a good response with small volume residual disease on CT scan in the para-aortic region only. He underwent para-aortic node dissection and one nodule was histologically positive. New inguinal adenopathy was also noted at operation. He received extensive radiotherapy to multiple sites but unfortunately progressed and died 10 months after first treatment.

Embryonal rhabdomyosarcoma. ***Cases 1–3.*** All presented with paratesticular disease, SIOP stage 1, and all underwent orchidectomy.

Case 1. Received six cycles of VAC chemotherapy followed by irradiation to para-aortic and ipsilateral pelvic nodes to 40 Gy in 20 fractions. He remains in CR with 2 years of follow-up.

Case 2. Received adjuvant VAC (with actinomycin replacing adriamycin after six cycles) for 1 year. He remains in complete remission after 9 years of follow-up.

Case 3. Initially managed with a "watch policy" for three months and then relapsed in para-aortic nodes. He underwent para-aortic node dissection and six cycles of VAC chemotherapy. One year later he had a second relapse, this time with multiple lung metastases and underwent thoracotomy. This was followed by five cycles of treatment with cisplatinum (20 mg/m^2 and ifosfamide 1.2 G.m^2) and 50 Gy "postage stamp" radiotherapy to lung metastases. He achieved complete remission and remains well 5 years later.

Case 4. A 22-year-old male presented with a psoas mass invading spinal cord (SIOP stage III). After decompressive surgery he received eight cycles of VAC chemotherapy, followed by high dose melphalan 200 mg/m^2 and autologous bone marrow transplant. He also received 45 Gy local radiotherapy to the left psoas. He achieved a good partial remission. He relapsed 14 months after completion of treatment both with local disease and multiple lung metastases. Further chemotherapy was given with no response and he died 3 years after initial treatment.

Case 5. A 32-year-old male presented with a pancreatic mass with bone marrow, skin and nodal involvement (SIOP stage IV). The initial diagnosis on bone marrow aspirate was anaplastic carcinoma and he received five cycles of BEP (bleomycin, etoposide and cisplatin, as for germ cell tumour), with a good response in the abdomen and skin. The correct diagnosis was made on repeat bone marrow and he then received six cycles of VAC chemotherapy. He maintained a good partial response but the disease persisted in the marrow and he relapsed with paraspinal disease in the thorax 1 month after completion of chemotherapy and died 1 month later, 6 months after initial treatment.

Nephroblastoma

Two adult patients were treated during the study years, compared with 33 patients treated by the Paediatric Department. Both were stage IV at presentation.

Case 1. A 36-year-old male presented with disease in the kidney, a solitary lung metastases and abnormal liver function tests. He was treated with nephrectomy followed by combination chemotherapy, consisting of actinomycin D, adriamycin, vincristine and cyclophosphamide which was given for six cycles. Radiotherapy was then given to the left renal bed to a dose of 42 Gy in 14 fractions. He achieved a good partial response but liver function tests remained abnormal.

He relapsed 4 months after radiotherapy in lung and bladder, and underwent resection at both sites followed by six cycles of VAC chemotherapy. Subsequently, he underwent megatherapy with high dose melphalan (200 mg/m^2) and autologous bone marrow transplant. Only a partial response was achieved but with residual tumour in the bladder. The disease progressed and he died 2 years and 8 months after treatment.

Case 2. A 23-year-old male presented with disease in the kidney, multiple lung metastases and abnormal liver function tests. He received the same chemotherapy as case 1 and was planned to receive radiotherapy to the renal bed and whole lung. Unfortunately the pulmonary metastases progressed on chemotherapy which was therefore discontinued after two cycles. Further chemotherapy was attempted but he died 4 months post-treatment, and at postmortem extensive disease was found in lungs, liver, lymph nodes and inferior vena cava.

DISCUSSION

The discussion will first address medulloblastoma and Ewing's sarcoma and then the subject of embryonal tumours in adults in general.

Medulloblastoma

The actuarial survival at 5 and 10 years for the group of adult patients reported here is 80% and compares very favourably with children treated over the same time period at this hospital and with other published series from the same era [6,7]. The patients in the present series overlap with a previous report from this hospital (1952–1981) [8] and other recent adult series report similar survival figures [9,10].

The presenting features, with an excess of male patients (12 out of 15) and of lateral tumours (11 out of 15), are in accord with many [11,12] but not all [9,10] adult series. Imageable neuraxis disease appears to be an adverse prognostic factor in children [13], although the significance of positive cytology has not been formally established. All three patients in this series who were noted to have positive cytology relapsed.

It was the policy to offer maintenance chemotherapy to all patients and therefore patients who were fit to receive it were likely to have a better prognosis. This may explain why patients who received maintenance chemotherapy had a better outcome than those who did not and the role of maintenance chemotherapy in adults with medulloblastoma remains undefined. The role of chemotherapy for children with medulloblastoma has not been established but a benefit is suggested at least in certain subgroups from randomised studies looking at survival as an endpoint [6,7].

The management of the relapsed patients is interesting: five patients relapsed, three within the central nervous system and two in the bone marrow alone, consistent with the results of Rochkind et al. [14] who found that bone was the commonest site of metastasis outside the central nervous system. Three of these patients were salvaged with VAC chemotherapy, two with the addition of high dose melphalan and one with further radiotherapy. Chemotherapy has previously been reported to be of palliative use in relapsed adult medulloblastoma [15]. Amongst the long-term survivors there are no treatment complications and quality of life is generally good.

Ewing's Sarcoma

The presenting features of this group of patients were unusual, with only five out of 15 occurring in the pelvis, femur, tibia and fibula, sites which account for 60% of primaries in paediatric practice [16]. In addition, four out of the 15 patients had extraosseous primaries, an uncommon finding in children. At presentation five patients had metastatic disease, at the upper end of the range expected from paediatric practice of 15%–35% [17,18]. The sites of these metastases were equally split between lung, bone marrow and lymph nodes; the last is a relatively unusual site in children. At first relapse, however, lung was the commonest site in this series. Two patients were initially misdiagnosed as non-Hodgkin's lymphoma, emphasising the difficulty of establishing the diagnosis of Ewing's, particularly in an adult setting.

The management of this group of patients was nonuniform, but generally reflected "current" paediatric practice, at the time, for those patients who were referred to The Royal Marsden Hospital for their primary management. There were three long-term survivors; all three had a low tumour burden. This was completely excised in two and was then followed by radical radiotherapy and prolonged systemic therapy, whilst the third patient had a biopsy and radiotherapy only. Comparison with known prognostic factors for children [14] is therefore difficult. Relapse-free survival of this group of patients is disappointing, particularly as the majority of patients had "good prognosis disease" with small volume peripheral tumours. Perhaps this reflects the problems of either

treating patients without standardised protocols or of applying such a protocol but in isolation.

GENERAL DISCUSSION

Embryonal tumours in adults are currently largely neglected but warrant more attention on two counts, namely, clinical management and tumour biology. In order to improve results of the former and expand knowledge of the latter, there is a requirement for central registration and data collection. For example, in the current series, variations have emerged between tumours arising in adults and those developing in children in terms of presenting features and treatment related history. However, patient numbers are small and these findings need to be confirmed by collaborative data collection. The recognition of a different pattern of behaviour when these tumours arise in adults would raise significant questions with regard to management, in terms of the appropriateness of applying paediatric protocols and the requirements for modification of therapy. It would also raise important questions regarding tumour biology, and invites speculation as to why different behaviour might be seen in an older population or after a longer "latency."

Although the initial scrutiny might imply different tumour biology, laboratory studies need to be applied in order to identify the existence and nature of any such variations. There has been a recent expansion in this approach to categorising tumours and identifying subtypes, which is currently being extended to embryonal tumours.

Because the majority of embryonal tumours occur in children, clinical and laboratory research is being initiated and performed from within the paediatric oncology organisations around the world. It would seem that data on embryonal tumours in adults could be most efficiently collected through the systems already in operation for children and that this data could be most useful when analysed in conjunction with the paediatric data. Although the National Wilms' Tumour Study Group has undertaken this task, it is not generally being taken on board by the paediatric oncology groups and as a result, a valuable source of clinical and biological information may be being discarded.

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